Retrospective Analysis of Tissue Plasminogen Activator as an Adjuvant Treatment for Calciphylaxis

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Objective: To report our experience with low-dose tissue plasminogen activator in the treatment of calciphylaxis, a rare, usually fatal thrombotic condition that results in ischemia, necrosis, and infarction of adipose and cutaneous tissue.

Design: Retrospective chart review.

Setting: Tertiary care academic medical center.

Patients: Fifteen patients (4 men and 11 women) with calciphylaxis, treated from January 1, 2002, through December 31, 2010.

Intervention: Treatment with tissue plasminogen activator, concomitant wound care, and management of calcium-phosphate status.

Main Outcome Measures: Short-term ulcer healing, long-term survival.

Results: Patients received daily low-dose infusions of tissue plasminogen activator (mean treatment duration, 11 days). Six patients had no adverse reactions, 3 had minor bleeding, 6 required blood transfusions, and 3 had life-threatening bleeding. No patients died of treatment-related complications. Ten patients died (median time to death, 3.6 months; range, 23 days to 4.2 years). Of the remaining 5 patients, the median duration of follow-up was 36.8 months (range, 70 days to 4.3 years). Patients treated with tissue plasminogen activator had approximately 30% greater survival than controls, but the difference was not significant ($P = .14$). Our results were limited by the use of concomitant therapies, referral bias for advanced disease, and retrospective case-series design.

Conclusions: Thrombolytic tissue plasminogen activator may be a useful adjunctive treatment in the management of patients with calciphylaxis. However, a multidisciplinary approach that includes aggressive wound care, débridement, thrombolytic therapy, restoration of tissue oxygenation, avoidance of infection, and control of calcium-phosphate homeostasis also is essential.


Calciphylaxis is a rare but morbid syndrome of painful subcutaneous nodules and necrotic ulcerations of the skin that occurs in up to 4% of patients receiving long-term dialysis. The diagnosis of calciphylaxis portends a very poor prognosis, with a median survival of 2.6 months from the date of diagnosis. Luminal narrowing by medial calcification and subintimal fibrosis of subcutaneous arterioles leads to thrombotic occlusion, cutaneous ischemia, and necrotic ulceration. Wound infection and sepsis are the most frequent causes of death. Restoration of blood flow is a most critical intervention.

Tissue plasminogen activator (tPA), a thrombolytic agent approved by the US Food and Drug Administration for acute myocardial infarction, is an effective treatment for coagulopathic disorders of the skin microvasculature, including livedo vasculopathy and antiphospholipid antibody syndrome. Our approach in treating calciphylaxis is to decrease calcium deposition, restore blood flow and oxygenation to the tissues, and provide aggressive wound care with débridement of necrotic tissue. In 2004, Sewell et al published our group’s first case report of calciphylaxis treated successfully with tPA. Herein, we report 14 additional cases.

Methods

Data collection

This retrospective study was approved by the Mayo Clinic Institutional Review Board. Our hospital database was reviewed, and patients who received a diagnosis of calciphylaxis and
were treated with tPA from January 1, 2002, through December 31, 2010, were included in the study. The patient described in the original 2004 case report was included in this series for the purpose of long-term follow-up. Electronic medical records were reviewed, and the following data were abstracted: sex, age at time of treatment with tPA, history of renal or liver disease, symptom duration, distribution of lesions, obesity, skin biopsy findings, relevant laboratory screening tests for a hypercoagulable state, prior and concomitant therapies, clinical course, adverse events, and survival. Assumed surviving patients were sent a follow-up questionnaire.

**TREATMENT**

All patients with calciphylaxis initially were admitted to the hospital (Mayo Clinic, Rochester, Minnesota) to a primary care service and followed up by the dermatology service and a multidisciplinary consultative group. The dermatology service oversaw wound care and managed the tPA protocol. Consultative services included nephrology, endocrinology, plastic surgery, hyperbaric oxygen specialists, pain service, physical medicine, infectious diseases, and vascular medicine.

Before initiating treatment, the diagnosis and prognosis of calciphylaxis were discussed with the patient and family. Risks of tPA treatment, including risk of life-threatening internal bleeding, were emphasized and weighed against the prognosis. Other treatment options such as sodium thiosulfate were reviewed at that time.

Low-dose tPA (alteplase; Genentech, San Francisco, California) was administered according to the protocol used for other cutaneous vaso-occlusive disorders. Hyperbaric oxygen therapy, depending on availability, was provided on an outpatient basis after completing the tPA protocol. Patients received ancillary treatments for wound care and débridement of necrotic tissues (eg, antisepptic wet dressings, whirlpool, or operative surgical or maggot larval débridement). If patients were undergoing dialysis, the nephrologists generally used a low-calcium dialysate, as previously described. Other treatments administered concurrently included cinacalcet or sodium thiosulfate.

**SURVIVAL**

Survival of patients with calciphylaxis treated with tPA was compared with survival of 63 patients with calciphylaxis who were not treated with tPA. The second cohort also was from our institution; this group was described by Weenig et al in 2007, and the follow-up information was updated as part of the current study. Survival rates were calculated using the Kaplan-Meier method and compared between the 2 groups using a 2-sided log-rank test. P values less than .05 were considered statistically significant.

**RESULTS**

Fifteen patients (11 women, 4 men) with a diagnosis of calciphylaxis treated with tPA were identified. The diagnosis was made by clinicopathologic correlation in 13 patients (all biopsy findings were consistent with calciphylaxis). Vascular thrombosis was noted in 6 of the 13 biopsy specimens. In 2 patients, the diagnosis was established on the basis of clinical findings alone.

The clinical lesions of calciphylaxis were generally located proximally in areas of high adipose content. Patients presented initially with deep, tender, firm, indurated plaques with surrounding livedo racemosa. The plaques typically progressed to hemorrhagic bullae, followed by large deep ulcerations with thick, necrotic, adherent eschar.

As listed in the Table, 10 of 11 women and 1 of 4 men were obese. In all cases, the areas of induration and ulceration involved the lower extremities; some patients had involvement of the upper extremities (n = 3) and the torso (n = 4). The body surface area (BSA) involved was estimated by considering the palm as approximately equivalent to 1% BSA. Two of the 3 patients with mild involvement (≤5% BSA) were alive at last follow-up (0.2 and 4.3 years). The 2 patients with extensive involvement (50%-60% BSA) died during hospitalization. All patients had calciphylaxis develop in the setting of renal failure. Twelve were undergoing dialysis, and 2 had a history of acute renal failure that resolved (1 requiring dialysis). Eleven of the 12 patients tested had coagulation abnormalities.

The duration of tPA infusion ranged from 1 to 14 days (mean, 11 days). Of the 15 patients who received tPA, 6 had no adverse reactions, 3 had minor bleeding, and 3 had major bleeding (gastrointestinal tract, retropertioneal, and subdural hematoma). Six patients required blood transfusions. No patient died as a result of hemorrhage or tPA treatment.

Twelve of the 13 hospitalized patients had improvement in their wounds: 4 had complete healing, 6 had partial healing, and 2 had stabilization. Only 1 had worsening wounds. Indicators of improvement included decreased pain or decreased use of pain medication as well as decreased livedo, erythema, and subcutaneous induration. Pretreatment and long-term follow-up images of 2 patients are shown in Figure 1 and Figure 2.

Survival curves for patients who received tPA and patients who received other treatments are shown in Figure 3. Among the 15 treated patients, 10 died during the study period (median time from diagnosis to death, 3.6 months; range, 23 days to 4.2 years). Because many of the patients died outside of our institution, causes of death are unknown. Among the 5 patients alive at last follow-up, the median duration of follow-up was 36.8 months (range, 70 days to 4.3 years). Of the 63 untreated patients previously studied at our institution, 52 died during the study period, with a median time to death of 2.6 months (range, 1 day to 11 years). For the remaining 11 patients, the median duration of follow-up was 5.7 months (range, 1 day to 12.5 years). The median age at diagnosis was 59 years in both groups. We observed improved survival among patients who were treated with tPA, but this difference did not reach statistical significance; we calculated a 14% probability that the observed difference between tPA-treated and untreated subjects was due to chance (P = .14).

**COMMENT**

Calciphylaxis is a painful ischemic disease of the subcutaneous vasculature that requires an accurate diagnosis. Medial arteriolar calcification alone is insufficient for di-
agnosing calciphylaxis on a histopathologic basis because it is a frequent finding in long-term renal failure and may be observed in patients with peripheral vascular disease (PVD). Lesions of calciphylaxis principally affect proximal and truncal areas of the body, where the fat content is higher, and usually present as multiple lesions at different stages of evolution. Calciphylaxis and PVD should be clinically differentiated from each other because their treatments and prognoses are different.12,13 A solitary necrotic ulcer on the shin that lacks expansion or development of new lesions on a daily basis.

Progression of calciphylaxis can be rapid, with expansion or development of new lesions on a daily basis. Our data suggest that the lower the BSA involved, the better the prognosis (Table). Biopsy, diagnosis, discussion with the patient and family, and decision making has to occur as soon as possible. Published reports about calciphylaxis treatments have been limited to case reports that focused on restoring calcium homeostasis with medications (sodium thiosulfate, cinacalcet) and parathyroidectomy.7-11 Sodium thiosulfate has anticoagulant and vasodilatory properties in addition to restoring calcium homeostasis. Some of our cohort had tried these treatments elsewhere before they were transferred to our institution owing to disease progression. Two survivors in our group had prior treatment with these agents; one continued to receive sodium thiosulfate with the tPA infusions and also received hyperbaric oxygen therapy.

The rationale for initiating tPA therapy is to address the thrombotic component of the disease.14 Some evidence, as shown in our cohort (Table), also suggests that a systemic hypercoagulable state may have a role in the pathogenesis of calciphylaxis, presumably by increasing the probability of thrombus formation.14,15 Because it lyses clots and restores blood flow, tPA therefore may be required in calciphylaxis treatment,16,17 similar to our group's previously recommended approach.5

Comparison of the survival data of 63 patients who did not receive tPA treatment with survival data of the patients who received tPA treatment showed approximately 30% improvement in survival for the tPA cohort (Figure 3), although the difference was not statistically significant. None of the surviving patients had greater than 20% BSA affected, indicating that limited extent of disease may be an important factor favoring survival.16 The only other parameter previously shown to favor survival was surgical débridement.2,18,19

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Symptom Duration, mo</th>
<th>Involved BSA, %</th>
<th>Renal Statusa</th>
<th>Hypercoagulation Risk Factorsb</th>
<th>Prior Therapy</th>
<th>Concurrent Therapy</th>
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<tr>
<td>1/F/68</td>
<td>5</td>
<td>Trunk, thighs</td>
<td>10-20</td>
<td>ESRD, HTN</td>
<td>LA</td>
<td>Surgical DB, wound therapy</td>
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<td>2/F/28</td>
<td>5</td>
<td>Trunk, extremities</td>
<td>50</td>
<td>ESRD, GN</td>
<td>History of LA</td>
<td>WP, Na thios, hyperbaric O2, Warfarin</td>
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<td>3</td>
<td>Extremities</td>
<td>5</td>
<td>ESRD, DM</td>
<td>Protein C, FVL</td>
<td>WP, Na thios, hyperbaric O2, Warfarin</td>
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<tr>
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<td>Extremities, Thighs</td>
<td>20</td>
<td>ESRD, HTN</td>
<td>Protein C, antithrombin</td>
<td>WP, aspirin, pentoxifylline, hydroxychloroquine, prednisone</td>
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<td>5</td>
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<td>Protein C, protein S</td>
<td>Hyperbaric O2, Na thios, pentoxifylline</td>
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<tr>
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<td>Elevated homocystine, MTHFR mutation</td>
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<td>Protein C, protein S</td>
<td>Pamidronate, vitamin D</td>
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<td>CRF, HTN, DM</td>
<td>Protein S</td>
<td>Methotrexate, prednisone, Cinacalcet</td>
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<tr>
<td>11/F/63c</td>
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<td>Extremities</td>
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<td>Cinacalcet</td>
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<td>12/F/67</td>
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<tr>
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<td>20</td>
<td>ESRD, IgA</td>
<td>Not tested</td>
<td>ASWD, WP, maggot DB</td>
</tr>
</tbody>
</table>

Abbreviations: ASWD, antiseptic wet dressings; BSA, body surface area; CRF, chronic renal failure; DB, débridement; DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; FSGN, focal sclerosing glomerulonephritis; FVL, factor V Leiden heterozygous carrier; GN, glomerulonephritis; HTN, hypertension; IgA, immunoglobulin A nephropathy; KMoO4, potassium permanganate; LA, lupus anticoagulant; M, male; Na thios, sodium thiosulfate; O2, oxygen; WP, whirlpool.

aAll patients except for patients 9 and 10 were undergoing dialysis.

bFor cases marked with “protein C,” “protein S,” or “antithrombin,” these terms indicate deficiencies in activity or increased resistance to activity.

cPatient alive at last follow-up.
Although the survival results are encouraging, we acknowledge that the mortality rate was still high. Many patients in our series did very well while in the hospital, as shown by the short-term outcome data and the improvement in their ulcerations during hospitalization. However, we have been unable to determine whether the care after discharge was adequate. Some patients who were discharged to home did not receive adequate wound care proportionate to their disease and were susceptible to infection. Patient 15 returned for follow-up in 3 weeks with a *Candida* infection of the entire leg.

Another potential reason why patients do not do well after discharge may be associated with the use of warfarin as a maintenance anticoagulation agent. Many patients admitted to the hospital with calciphylaxis were already taking warfarin as new lesions continued to develop. Warfarin potentially enhances the process of vascular calcification and has been shown to do so in animal models. If not warfarin, what other anticoagulant can be used? Low-molecular-weight heparin may be another choice. Newer anticoagulants such as the antithrombin agent dabigatran may be of benefit, but they are not currently recommended for widespread use.

Additional studies are needed to validate the use of thrombolytic agents in calciphylaxis. Because calciphylaxis is a rare condition, prospective studies are difficult to perform. Improving standardization of patient protocols, using combination and multidisciplinary management, and ensuring continued and consistent home wound care can potentially improve outcomes.

Based on the results of this study, we recommend a process that considers several factors when selecting patients for the tPA protocol. Young or healthy patients who are motivated will likely fare better than older patients with extensive atherosclerotic disease and other comorbid conditions. Evaluating the severity of the disease by evaluating the area of involvement may be a helpful guide. Patients with an area about 5% to 15% BSA will also likely have better outcomes. In both of these assessments, the judgment of the physician in evaluating the patient as a whole is imperative. For example, an older patient with multiple comorbid conditions but 5% BSA involvement may do very well if
treated early. Early treatment before widespread involvement of the disease is likely to be associated with better outcomes. If the affected area is greater than 25% BSA, a different treatment option should be considered.

The limitations of the study include a lack of protocol standardization for patients receiving therapies concomitant with tPA, which limited our ability to determine the independent effect of tPA. This study may be affected by a referral bias for advanced disease, potentially diminishing the therapeutic benefit of earlier intervention. The qualitative assessment of wound improvement is inherent to a retrospective case-series study design. In conclusion, we present our protocol using tPA as an adjunctive thrombolytic agent in the treatment of calciphylaxis. We recommend long-term continued management of these patients after hospital discharge.

References


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Author Contributions: Drs el-Azhary and Arthur had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: el-Azhary, Davis, Gibson, and Weenig. Acquisition of data: el-Azhary, Arthur, Davis, McEvoy, Wetter, and Weenig. Analysis and interpretation of data: el-Azhary, Arthur, Davis, Gibson, Weaver, Camilleri, Wetter, and Weenig. Drafting of the manuscript: el-Azhary, Arthur, Davis, McEvoy, and Weenig. Critical revision of the manuscript for important intellectual content: el-Azhary, Arthur, Davis, McEvoy, Gibson, Weaver, Camilleri, Wetter, and Weenig. Statistical analysis: Weaver. Administrative, technical, and material support: el-Azhary, Davis, and Weenig. Study supervision: el-Azhary, Davis, McEvoy, Gibson, and Weenig. Conflict of Interest Disclosures: None reported.

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